

## SYNTHESIS OF [F-18]-1-AMINO-3-FLUOROCYCLOBUTANE-1-CARBOXYLIC ACID (FACBC): A PET TRACER FOR TUMOR DELINEATION

Timothy M. Shoup and Mark M. Goodman

Emory Center for Positron Emission Tomography,  
Emory University, Atlanta, GA 30322

### Summary

Fluorine-18 labeled 1-amino-3-fluorocyclobutane-1-carboxylic acid (FACBC), a new tumor-avid amino acid, was synthesized for positron emission tomography. [<sup>18</sup>F]FACBC was prepared with high specific activity by nucleophilic displacement with an overall radiochemical yield of 12% (EOB). Synthesis of the triflate precursor was accomplished in nine steps starting from the reaction of benzyl bromide with epichlorohydrin which gave 1-chloro-2-benzyloxy-3-bromopropane. A key step involves conversion of 3-benzyloxy-cyclobutane-1,1-dicarboxylate diamide to a mixture of diastereomeric 2-benzyloxycyclobutane hydantoins.

**Key Words:** PET, radiofluorine, amino acid, tumor imaging, hydantoin

### Introduction

It is crucial to delineate tumors, particularly of the brain, so that a surgical or local radiotherapeutic therapy can maximize lesion resection without destroying intact or functionally indispensable tissue. Anatomical imaging of tumors with CT and MRI are routinely used but they can not always distinguish between necrosis and recurrent tumor because both types of lesions may show contrast enhancement due to BBB damage and a mass effect (1-6).

Certain amino acids are required nutrients for cellular metabolism and their uptake is greater in cancer cells as a consequence of increased amino acid transport (7). Tumor cells proliferate rapidly and require large amounts of proteins to build the fast growing tissue. Because of this abnormally high rate of protein synthesis, measuring the rate of amino acid incorporation into cells has proved to be a more sensitive and specific, and therefore, a more reliable means of tumor detection than measuring cerebral glucose uptake with PET or enhanced CT scanning (6).

We have developed 1-amino-3-fluorocyclobutane-1-carboxylic acid (FACBC) (10) labeled with fluorine-18, an unnatural, nonmetabolized amino acid (8-13) which potentially can have widespread use as a diagnostic imaging agent for visualizing malignant tumors. This new agent represents the first fluorinated analog of ACBC, an amino acid known to have tumor specificity (8,14). [ $^{18}\text{F}$ ]FACBC was prepared with high specific activity (no carrier added) and was evaluated for its potential in tumor localization (15). [ $^{18}\text{F}$ ]FACBC showed high tumor uptake in rats implanted intracerebrally with 9L gliosarcoma cells. PET imaging has revealed a 6 to 1 tumor-to-normal brain ratio of [ $^{18}\text{F}$ ]FACBC in a patient with residual glioblastoma multiforme. Herein, we provide the details of the synthesis of [ $^{18}\text{F}$ ]FACBC (10) and FACBC (12).

### Results and Discussion

Synthesis of [ $^{18}\text{F}$ ]FACBC (10) was accomplished in ten steps as outlined in Figure 1. 1-Chloro-2-benzyloxy-3-bromopropane (1) was prepared in 60% yield by treatment of epichlorohydrin with benzyl bromide and mercurous chloride (16). Formation of diethyl 3-benzyloxy-3-cyclobutane-1,1-dicarboxylate (2) was achieved in 55% yield by treating diethyl malonate with sodium hydride followed by addition of 1-chloro-2-benzyloxy-3-bromopropane and refluxing for several days (16). Stirring diester 2 in concentrated ammonium hydroxide provided the corresponding 3-benzyloxy-3-cyclobutane-1,1-dicarboxamine (3) which was then converted to a mixture of 3-benzyloxy-3-cyclobutane hydantoins (4) (75:25 diastereomeric ratio) in 60% yield using dilute sodium hypochlorite (17). This reaction proceeds presumably via a N-dichlorodiamide, which in the presence of base, undergoes a Hofmann rearrangement affecting only one of the amide moieties to give the hydantoin (18). In our reaction, the predominate isomer possesses syn benzyloxy-amide groups. It is interesting that formation of the hydantoin is diastereoselective. When 3-fluorocyclobutane-1,1-dicarboxamine was treated with dilute sodium hypochlorite a 50:50 mixture of diastereomeric 3-fluorocyclobutane hydantoins was formed. Hence, it may be possible to increase selectivity further by using the appropriate C-3 substituent on 3. Hydrolysis of the hydantoins, using the method of aqueous barium hydroxide at reflux (11), gave low yields of the benzyloxy amino acid. Instead, a 76% yield of 1-amino-3-benzyloxy-3-cyclobutane-1-carboxylic acid was obtained by heating the hydantoin in a solution of ammonium carbonate contained in a sealed gas cylinder at 170°C for 6 hours.

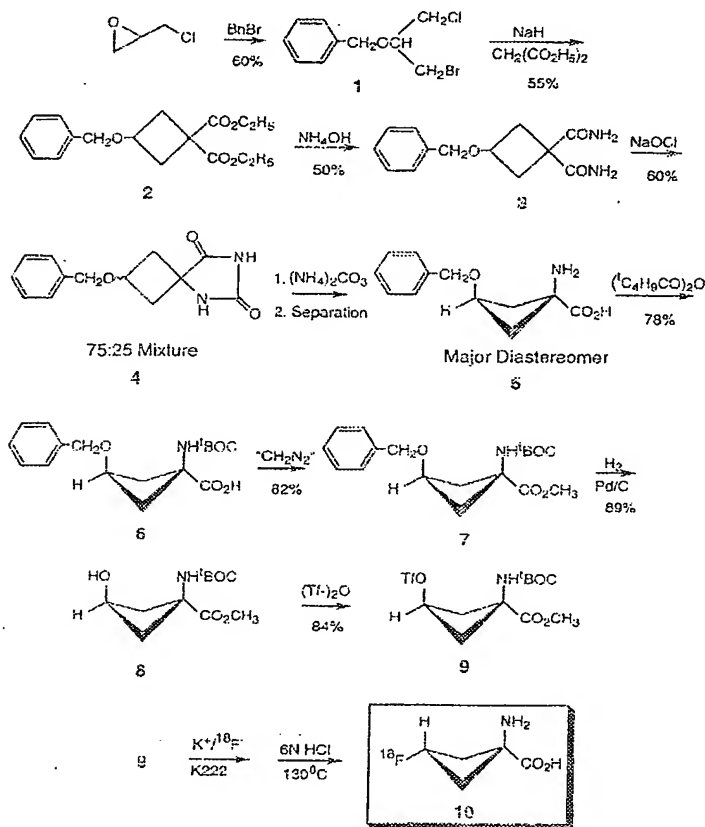


Figure 1. Synthesis of [ $^{18}\text{F}$ ]FACBC

Diastereomeric amino acids were separated by reverse phase HPLC using 0.9% saline/methanol (80:20) solvent. Protection of the amino acid moiety was accomplished in two steps first by using di-*tert*-butyl dicarbonate to form *t*-butyl-carbamate 6 followed

by treatment with diazomethane, derived from 1-methyl-3-nitro-1-nitrosoguanidine and base, to give the corresponding 1-*t*-butyl carbamate-3-hydroxy-1-cyclobutane-1-carboxylic acid methyl ester (7) in 82% yield. After debenzylation using hydrogen and 10% palladium on charcoal (50% wet Degussa type), the resultant 1-*t*-butyl carbamate-3-hydroxy-1-cyclobutane-1-carboxylic acid methyl ester (8) was converted to trifluoromethyl sulfonate 9 in 84% yield using trifluoromethane sulfonic anhydride and pyridine. The stereochemical assignment for the predominant amino acid was determined by X-ray crystallography on 8.

No-carrier-added radiofluorination of 1-*t*-butyl carbamate-3-trifluoromethane sulfonyloxy-1-cyclobutane-1-carboxylic acid methyl ester (9) was performed at 85°C for 5 min using dried [ $^{18}\text{F}$ ]fluoride, potassium carbonate and Kryptofix in acetonitrile. Extending the reaction times to 10 and 15 min did not increase [ $^{18}\text{F}$ ]fluoride incorporation and higher reaction temperatures (100°C and 115°C) resulted in 10-20% lower yields. Following passage of the reaction mixture through a silica Sep Pak to remove unreacted [ $^{18}\text{F}$ ]fluoride, deprotection of [ $^{18}\text{F}$ ]-1-*t*-butyl carbamate-3-fluoro-1-cyclobutane-1-carboxylic acid methyl ester was achieved by acid hydrolysis to yield [ $^{18}\text{F}$ ]FACBC (10). Synthesis of 10 was completed in 60 min following EOB with an overall radiochemical yield of 12% (EOB).

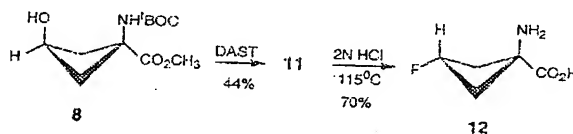


Figure 2. Synthesis of FACBC

Synthesis of "cold" FACBC (12, Figure 2) involved treatment of 1-*t*-butyl carbamate-3-hydroxy-1-cyclobutane-1-carboxylic acid methyl ester (8) with DAST in a 50/50 mixture of methylene chloride and DG at 80°C which gave 11 in a 44% yield. The fluorinated intermediate 11 was hydrolyzed using 2N HCl for 3 hrs. The aqueous solution was passed through a AG-11 AR mixed bed exchange resin using water to elude FACBC. It must be noted that during an alternative route to FACBC in which the

3-fluorocyclobutane hydantoin was used, base hydrolysis resulted in defluorination of the fluorohydantoin.

#### Materials and Methods

Analysis for carbon and hydrogen was performed by Atlantic Microlab Inc., Norcross, GA. Melting points were measured with a Electrothermal 9100 apparatus (Electrothermal Eng. Ltd.) and are uncorrected. Proton NMR spectra were acquired with a GE QE PLUS 300 instrument; the chemical shifts are reported in parts per million (delta) down field from tetramethylsilane. All reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI) and were used without further purification. Thin layer chromatography was performed on Silica gel AL SIL G/UV 250  $\mu$ m plates (Whatman Ltd, Kent, England). Column chromatography was accomplished on Silica gel Merck grade 9383, 230-400 mesh, 60A (Aldrich Co.) using the solvent as indicated. Chromatograms of the radiolabeled compounds were analyzed with a Bioscan System 200 (Washington, D.C.) on either silica gel AL SIL G/UV 250  $\mu$ m plates or 0.25 mm RP Chiralplates (Macherey-Nagel from Alltech Co., Deerfield, IL).

#### Synthesis of [F-18]-1-amino-3-fluoro-cyclobutane-1-carboxylic acid (FACBC).

*1-Chloro-2-benzyloxy-3-bromopropane* (1). Using the procedure of Michejda and Cornick (11), a mixture of benzyl bromide (46.2 g, 0.27 mol), epichlorohydrin (25 g, 0.27 mol), and 45 mg of mercurous chloride was heated for 12 hr at 150°C. Distillation through a 12-in Vigreux column yielded 42.5 g (60%) of 1-chloro-2-benzyloxy-3-bromopropane; bp 150-155 (0.5 mm) (lit. (11) bp 142-145°C, 0.3 mm);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.34-3.9 (m, 4H,  $\text{CH}_2$ ), 4.58 (s, 2H, O- $\text{CH}_2$ ), 7.26 (s, 5H, phenyl).

*Diethyl 3-benzyloxycyclobutane-1,1-dicarboxylate* (2) (11). To a stirred slurry of 4.6 g (0.19 mol) of sodium hydride in 115 mL of dry dioxane was added dropwise 30.4 g (0.19 mol) of diethyl malonate over a 30 min period. After this addition was complete, 50.0 g (0.19 mol) of 1-chloro-2-benzyloxy-3-bromopropane was added dropwise in 30 min. The mixture was heated at reflux for 44 hr, cooled to room temperature, and 4.6 g (0.19 mol) of sodium hydride in 50 mL of dioxane was added in portions. The mixture was heated at reflux for an additional 120 hr. The solvent was partially removed under

reduced pressure and the mixture was treated with 100 mL of water. The organic layer was extracted into ether. The ether extracts were dried and concentrated and the residue was distilled under reduced pressure. Distillation through a 12-in Vigreux column yielded 32.1 g (55%) of diethyl 3-benzyloxycyclobutane-1,1-dicarboxylate; bp 165-170°C (0.5 mm) (lit. (11) 174-176°C, 0.9 mm);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.23 (t,  $J=7\text{ Hz}$ , 6H,  $\text{CH}_3$ ), 4.0-4.7 (m, 1H OCH), 4.34 (s, 2H OCH<sub>2</sub>), 4.13 (q,  $J=7\text{ Hz}$ , 4H, OCOCH<sub>2</sub>), 7.23 (s, 5H, phenyl).

*3-Benzyloxycyclobutane-1,1-dicarboxamine* (3). Diethyl 3-benzyloxycyclobutane-1,1-dicarboxylate (2) (20 g, 65 mmol) was stirred with concentrated aqueous ammonia (250 mL) for four days at room temperature. The diamide was collected by filtration and washed with water followed by ethyl acetate. The yield of 3 was 8.1 g (50%); mp 200-203°C;  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  2.2 (m, 2H, CH<sub>2</sub>), 2.5 (m, 2H CH<sub>2</sub>), 3.8 (q,  $J=7.2\text{ Hz}$  1H OCH), 4.3 (s, 2H, OCH<sub>2</sub>), 7.0 (m, 4H, NH<sub>2</sub>), 7.23 (s, 5H, phenyl). Anal calcd. for  $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_3$  (248.28): C, 62.89; H, 6.50. Found: C, 62.67; H, 6.82.

*5-(3-benzyloxycyclobutane)hydantoin* (4). 3-Benzyloxycyclobutane-1,1-dicarboxamine (3) (2.0 g, 8 mmol) was stirred in 150 mL of dilute sodium hypochlorite (Aldrich product/water 1 to 2) at 0-5°C for 4 hr. The reaction mixture stood over night at room temperature. Unreacted diamide was recovered by filtration. The solution was neutralized to pH 5 with concentrated hydrochloric acid and evaporated to dryness. The residue was extracted with 50 mL of hot methanol, filtered, and filter cake was washed with 50 mL of hot methanol. The methanol solutions were combined and evaporated. Chromatography of the crude solid on silica gel using  $\text{CH}_2\text{Cl}_2$ /methanol (95:5) afforded 1.2 g (60%) of a 75:25 mixture of diastereomeric hydantoins 4; mp for major isomer: 166-168°C; mp for minor isomer: 190-194°C. The isomer ratio was determined before chromatography by reverse phase HPLC (C18, methanol/ water 50:50).  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  2.2 (m, 2H, CH<sub>2</sub>), 2.6 (m, 2H CH<sub>2</sub>), 3.99 (q,  $J=7.2\text{ Hz}$  1H OCH), 4.3 (s, 2H, OCH<sub>2</sub>), 4.39 (s, 2H, OCH<sub>2</sub>), 8.2 (s, 1H, NH), 7.29 (br s, 5H, phenyl), 10.6 (s, 1H, NH). Anal calcd. for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3$  (246.27): C, 63.40; H, 5.73. Found: C, 63.19; H, 5.90.

**1-Amino-3-benzoyloxycyclobutane-1-carboxylic acid (5).** A mixture of hydantoins 4 (1.0 g, 4.1 mmol) was hydrolyzed by heating with 65 mL of a 30% aqueous solution of ammonium carbonate in a closed gas cylinder (cap. 80 mL) at 160-170°C for 6 hrs. The solution was neutralized to pH 6 with conc. HCl and evaporated to dryness. The residue was extracted with 50 mL of hot methanol, and filtered. Yield: 0.69 g (76%). Reverse phase HPLC was used for separation of isomers: 25x10 mm Waters C<sub>18</sub> prep column, flow=15 mL, Rt=14 min (minor isomer) and 16 min (major isomer); solvent: 0.9% saline/methanol 75:25. HPLC separation yielded 0.10 g (11%) of the minor isomer and 0.27 g (30%) of the major isomer. The hydrolysis reaction was repeated until a sufficient quantity of pure isomer 5 was obtained. Decomposition 220-223°C; <sup>1</sup>H NMR (d<sub>4</sub>-methanol) δ 2.2-2.9 (m, 4H, CH<sub>2</sub>), 4.3 (t, J=6.9 Hz, 1H, OCH), 4.5 (s, 2H, OCH<sub>2</sub>), 7.23 (br s, 5H, phenyl). Anal calcd. for C<sub>12</sub>H<sub>15</sub>NO<sub>3</sub> (221.26): C, 65.14; H, 6.33. Found: C, 65.26; H, 6.48.

**1-*t*-Butyl carbamate-3-benzoyloxy-1-cyclobutane-1-carboxylic acid (6).** A solution of diastereomerically pure amino acid 5 (0.5 g, 2.3 mmol) in 10 mL of a mixture of methanol/triethylamine (90: 10) was treated with 1.0 g (4.6 mmol) of di-*tert*-butyl dicarbonate. The mixture was heated at 50-60°C for 10 min and then the solvent was removed by rotoevaporation. The crude oil was chromatographed on Silica gel using methylene chloride/methanol (95 to 5) with 0.1% formic acid. The product 6 (0.56 g, 76%) showed a single spot on TLC (Rf=0.59) with the same solvent system; mp 153-155°C; visualization was with MoO<sub>3</sub>-H<sub>3</sub>PO<sub>4</sub>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.35 (s, 9H, CH<sub>3</sub>), 2.27-2.88 (m, 4H, CH<sub>2</sub>), 4.18 (m, 1H, CHO), 4.42 (s, 2H, OCH<sub>2</sub>), 7.23 (br s, 5H, phenyl). Anal calcd. for C<sub>17</sub>H<sub>23</sub>NO<sub>5</sub> (321.37): C, 63.54; H, 7.21. Found: C, 63.24; H, 7.45.

**1-*t*-Butyl carbamate-3-benzoyloxy-1-cyclobutane-1-carboxylic acid methyl ester (7).** To a slurry of 1-methyl-3-nitro-1-nitrosoguanidine (150 mg) in 8 mL of ether at 0-5°C was added a 40% solution of potassium hydroxide dropwise. The resultant diazomethane ether solution was added to 0.15 g (0.50 mmol) of 6 in 3 mL of ether and the mixture was stirred at room temperature for 15 min. The ether was evaporated and the crude residue was chromatographed on Silica gel using ethyl acetate/hexane (1 to 9). Yield: 0.13 g (82%) of an oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.35 (s, 9H, CH<sub>3</sub>), 2.27-2.88 (m, 4H, CH<sub>2</sub>),

3.72 (s, 3H, CH<sub>3</sub>), 4.18 (m, 1H, CHO), 4.42 (s, 2H, OCH<sub>2</sub>), 7.23 (br s, 5H, phenyl). Anal calcd. for C<sub>18</sub>H<sub>25</sub>NO<sub>5</sub> (335.40): C, 64.46; H, 7.51. Found: C, 64.31; H, 7.78.

*1-t-Butyl carbamate-3-hydroxy-1-cyclobutane-1-carboxylic acid methyl ester (8).* A solution of 0.10 g (0.3 mmol) of the protected amino acid benzyl ether 7 in 10 mL of methanol was stirred with 25 mg of 10% palladium on charcoal (50% wet Degussa type). The mixture was stirred under a positive pressure of hydrogen (balloon) for 16 hr. The mixture was filtered through Celite and the solvent was evaporated. The crude residue was chromatographed on Silica gel using methylene chloride/methanol (9:1). The product 8 (65 mg, 89%) showed a single spot on TLC (R<sub>f</sub>=0.81) with the same solvent system; visualization was with MoO<sub>3</sub>-H<sub>3</sub>PO<sub>4</sub>; mp 128-129.6°C. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.41 (s, 9H, CH<sub>3</sub>), 2.05-2.9 (m, 4H, CH<sub>2</sub>), 3.6 (s, 3H, CH<sub>3</sub>), 4.28 (m, 1H, HCO). Anal calcd. for C<sub>11</sub>H<sub>19</sub>NO<sub>5</sub> (245.13): C, 53.87; H, 7.81. Found: C, 53.98; H, 7.65.

*1-t-Butyl carbamate-3-trifluoromethanesulfonyl-1-cyclobutane-1-carboxylic acid methyl ester (9).* Alcohol 8 (25 mg, 0.10 mmol) was dissolved in 10 mL of dry methylene chloride and pyridine (400 μL) by stirring under N<sub>2</sub>. The solution was cooled to 0-5°C and 120 μL of trifluoromethanesulfonyl anhydride was added. After 15 min, the solvent was removed in *vacuo* (no heating) and the crude oil was chromatographed on Silica gel (7" x 0.5") using ethyl acetate/hexane (3 to 7). Product 9 (32 mg, 84%) showed a single spot on TLC (R<sub>f</sub>=0.60) with the same solvent system; visualization was with MoO<sub>3</sub>-H<sub>3</sub>PO<sub>4</sub>.

*[<sup>18</sup>F]-1-Amino-3-fluoro-cyclobutane-1-carboxylic acid (10).* To a Wheaton 5-ml reaction vial containing approximately 500 mCi (20 μ amp, 60 min bombardment) in 350 mg of <sup>18</sup>O-water was added a 1 ml aliquot from a solution consisting of 125 mg Kryptofix, 25 mg potassium carbonate, 0.5 ml water and 12 ml acetonitrile. The solution was heated at 115°C and the solvent was evaporated with the aid of an Argon gas flow. Remaining moisture was removed by addition of 2 ml of dry acetonitrile to the vial followed by evaporation using Argon flow. This process was repeated 3 more times to ensure dryness of the fluoride. A solution of 1-t-butyl carbamate-3-trifluoromethanesulfonyl-1-cyclobutane-1-carboxylic acid methyl ester (9) (12 mg) in 500 μL of dry acetonitrile was introduced into the vial and the fluorination (no-carrier-added) reaction was performed

at 85°C for 5 min. The mixture was diluted with methylene chloride (1 mL) and unreacted  $^{18}\text{F}^-$  was removed by passage through a silica gel Sep-Pak. The Sep-Pak was rinsed with 6 mL of methylene chloride and the combined eluant was evaporated using an Argon flow that gave the  $^{18}\text{F}$  labeled intermediate (68 mCi) in 18% E.O.B. yield. Deprotection was achieved by using 0.5 mL of 6 N HCl at 130°C for 10 min. The aqueous solution containing 10 was passed through a 12 x 1.5 cm column of an ion-retardation resin (AG 11A8 50-100 mesh) in series with an alumina Sep-Pak (wet), a C18 Sep-Pak, and a 0.22  $\mu$  Millipore sterile filter using sterile water. The eluant containing 10 was collected in a sterile vial and made isotonic by addition of 0.96 mL of a 22.4% solution of sodium chloride. The synthesis was completed in 60 min following EOB with an overall radiochemical yield of 42 mCi (12% EOB). Radio-TLC showed 99% radiochemical purity (Chiralplates, 20:5:5 acetonitrile/water/methanol,  $R_f=0.63$ ). Radio-HPLC analysis (Zorbax reverse-phase C18, 4.6 mm x 250 mm, 0.1% acetic acid, flow rate 1 mL/min,  $t_r = 5$  min) showed [ $^{18}\text{F}$ ]FACBC to have a specific activity of at least 1.5 Ci/ $\mu$ mole. Chemical identity was confirmed by co-elution with reference compound 12 (HPLC-Waters 410 Differential Refractometer).

**Synthesis of 1-amino-3-fluoro-cyclobutane-1-carboxylic acid (FACBC).**

*1-t-Butyl carbamate-3--fluoro-1-cyclobutane-1-carboxylic acid methyl ester (11).* Alcohol 8 (150 mg, 0.6 mmol) was dissolved in 20 mL of a 50/50 mixture of dry methylene chloride and 2-methoxyethyl ether by stirring under  $\text{N}_2$ . The solution was cooled to -72°C (dry ice/acetone bath) and 109 mg (0.70 mmol) of diethylaminosulfur trifluoride was added. The mixture was allowed to warm to room temperature and it was then heat at 70°C for 3 hrs. The solvent was removed in *vacuo* and the crude oil was chromatographed on Silica gel using methylene chloride/methanol 95:5. Product 11 (67 mg, 45%, oil) showed a single spot on TLC ( $R_f=0.33$ ) with the same solvent system; visualization was with  $\text{MoO}_3\text{-H}_3\text{PO}_4$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.37 (s, 9H,  $\text{CH}_3$ ), 2.57-2.95 (m, 4H,  $\text{CH}_2$ ), 3.71 (s, 3H,  $\text{CH}_3$ ), 5.22 (d, quintet, 1H,  $J=56.4, 6.6$  Hz, CHF).

*1-Amino-3-fluoro-cyclobutane-1-carboxylic acid (12).* Hydrolysis of 11 (67 mg, 0.27 mmol) using 5 mL of 2 N HCl at 115°C for 2 hr followed by passed through an ion-retardation resin (10 g, AG 11A8 50-100 mesh) afforded an aqueous solution of the

fluoro-amino acid. The solution was concentrated and 12 was purified by HPLC (Waters C18 column: 25mm x 100mm, using 1% acetic acid in water, flow rate=7 ml/min, Rt=5 min). Decomposition 249°C. Yield 25.1 mg (70%).  $^1\text{H}$  NMR (deuterium oxide)  $\delta$  2.56-2.71 (m, 2H, CH<sub>2</sub>), 2.95-3.02 (m, 2H, CH<sub>2</sub>), 5.22 (d, quintet, 1H, J=56.4, 6.6 Hz, CHF). Anal calcd. for C<sub>5</sub>H<sub>8</sub>FNO<sub>2</sub> (133.12): C, 45.11; H, 6.06. Found: C, 45.01; H, 6.25.

#### X-ray Crystallography Experimental.

Compound 8, as a colorless plate with dimensions of 0.10 x 0.40 x 0.54 mm<sup>3</sup> was used for data collection. Intensity data were collected at room temperature on a Siemens P4 instrument and corrected for polarization, absorption and extinction. The structure was solved by direct methods and refined by full-matrix least-squares procedures on F<sup>2</sup> using SHELXL 93. All non-hydrogen atoms were refined anisotropically. The H atom of O1 was located from the difference map and refined isotropically unconstrained. All other H atoms were generated at calculated positions and were constrained using a riding model with isotropic thermal parameters that were 50% greater for the methyl H atoms, and 20% greater for the remaining H atoms than the U(eq) of the bonded heavy atom.

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